95. (New) The method of claim 63, wherein the adenoviral genome is a human adenoviral genome.

96. (New) The method of claim 95, wherein the adenoviral genome is an Ad5 adenoviral genome.

97. (New) The method of claim 65, wherein the adenoviral genome is a human adenoviral genome.

98. (New) The method of claim 97, wherein the adenoviral genome is an Ad5 adenoviral genome.

REMARKS

The Present Invention

The present invention provides a plasmid comprising a reading frame ORF6 of an E4 region of an adenovirus genome under the control of a heterologous inducible promoter. The present invention also provides a defective recombinant adenovirus that (a) requires, for replication, complementation *in trans* of one or more essential gene functions of an E1 region and an E4 region of an adenovirus genome, and (b) comprises an adenoviral genome having a deficiency of one or more essential gene functions of the E1 region, a deletion of the entire E4 region, and optionally a deletion of all or part of the E3 region. The present invention further provides a system and method useful for propagating a replication-deficient adenoviral vector.

The Pending Claims

Claims 44, 48, 50, 52-60, 63-70, and 73-98 are currently pending. Claim 44 is directed to the plasmid, while claims 48, 50, 52, 89, and 90 are directed to the defective recombinant adenovirus. Claims 53-60, 73-80, and 91-94 are directed to the system, while claims 63-70, 81-88, and 95-98 are directed to the method.

The Office Action

The Office Action raises the following concerns:

(a) Claims 53-61 and 63-71 are rejected under 35 U.S.C. § 101 for allegedly being drawn to inoperative subject matter.

(b) Claims 48 and 50-52 are rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description.

(c) Claims 53-61 and 63-71 are rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description.

(d) Claims 48, 49, 51-60, 62-70, and 72 are rejected under the judicially created doctrine of obviousness-type double patenting for allegedly being unpatentable over claims 1, 4, 7, 9-11, 14, 17, 19, and 22-24 of U.S. Patent 5,994,106.

(e) Claims 48-60, 62-70, and 72 are rejected under the judicially created doctrine of obviousness-type double patenting for allegedly being unpatentable over claims 1-10 of U.S. Patent 6,482,616.

(f) Claims 44 and 48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting for allegedly being unpatentable over claims 19, 20-26, 36-40, 43-56, 62-71, and 76-95 of copending U.S. Application No. 08/258,416.

(g) Claims 48-72 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting for allegedly being unpatentable over claims 36-38, 49, 51-54, 68-70, 72-76, and 109-114 of copending U.S. Application No. 09/261,922.

(h) Claims 48, 49, 51, and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting for allegedly being unpatentable over claims 36, 39, 40, 42, 44-46, 49, 50, 52, 54, and 55 of copending U.S. Application No. 09/934,207.

Reconsideration of these rejections is hereby requested.

The Claim Amendments

Claims 48, 50, 53, 55, and 63 have been amended to point out more particularly and claim more distinctly the present invention. Support for the amendments to claims 48 and 50 can be found in the specification at, for example, page 11, lines 26-31, and Examples 3 and 4. Claims 53 and 63 have been amended to delete reference to a 293 cell or an A549 cell, while the amendment to claim 55 serves to correct punctuation errors (i.e., insertion of a comma). Claims 73-98 are new. Support for claims 73-88 can be found in the specification at, for example, page 11, lines 26-31, page 13, line 27, through page 15, line 17, Examples 3-4, and Examples 8-10. Claims 89-98 are supported by the specification at, for example, page 11, lines 20-25. Accordingly, no new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the claims, as well as the text of the pending claims, are enclosed herewith.

Discussion of Rejection Under 35 U.S.C. § 101

Claims 53-61 and 63-71 have been rejected under Section 101 for allegedly encompassing subject matter that is "inoperative for practice" with 293 cells. In an effort to advance prosecution, and not in acquiescence of the rejection, claims 53 and 63 have been amended to delete reference to 293 cells. Thus, the Section 101 rejection is rendered moot by these amendments and should be withdrawn.

Discussion of Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 48 and 50-52, 53-61, and 63-71 have been rejected under Section 112, first paragraph, for an alleged lack of written description. These rejections are traversed for the reasons set forth below.

With respect to claims 48 and 50-52, the Office Action contends that the specification does not disclose the deletion of the entire E1 region, which, in addition to the E1A and E1B coding region, includes E1 regulatory regions (e.g., the E1A enhancer) and the pIX promoter and coding sequence, and overlaps the packaging sequence. In order to advance prosecution of the subject application, and as suggested by the Office Action, claim 48 has been amended to recite that the defective adenoviral vector comprises an adenoviral genome having a deficiency of one or more essential gene functions of the E1 region, while claim 50 has been amended to recite that the defective adenoviral vector comprises an adenoviral genome having a deficiency of all essential gene functions of the E1 region. Claim 51 has been cancelled, thereby mooting the Section 112, first paragraph, rejection of that claim.

Therefore, the subject matter of claims 48 and 50, as well as claim 52 depending therefrom, is adequately described in the present specification so as to convey to one of ordinary skill in the art that Applicants had possession of the claimed invention.

Claims 53-61 and 63-71 allegedly lack adequate description in the specification to convey to one of ordinary skill in the art that Applicants had possession of the claimed invention. In this respect, the Office Action contends that 293 cells cannot be used in an adenoviral vector propagation system and/or method in which there is no overlap between the adenoviral genome of an E1-deficient adenoviral vector and the genome of a corresponding E1-complementing cell line. As discussed with respect to the Section 101 rejection, claims 53 and 63 have been amended to delete reference to 293 cells. Thus, Applicants believe that the Section 112, first paragraph, rejection of claims 53-61 and 63-71 is rendered moot by these amendments.

Accordingly, claims 48, 50, 52, 53-61, and 63-71 are adequately described by the present specification. Thus, the Section 112, first paragraph, rejection should be withdrawn.

Discussion of Obviousness-Type Double Patenting Rejections

The Office Action has rejected claims 48, 51-60, 62-70, and 72 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 4, 7, 9-11, 14, 17, 19, and 22-24 of U.S. Patent 5,994,106 ("the '106 patent"). The Office Action also has rejected claims 48, 49, 50-60, 62-70, and 72 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-10 of U.S. Patent 6,482,616 ("the '616 patent"). Applicants submit herewith Terminal Disclaimers over the '106 patent and the '616 patent, thereby mooting the obviousness-type double patenting rejections.

Discussion of Provisional Obviousness-Type Double Patenting Rejections

Certain of claims 44-72 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 19, 20-26, 36-40, 43-56, 62-71, and 76-95 of U.S. Application No. 08/258,416, claims 36-38, 49, 51-54, 68-70, 72-76, and 109-114 of U.S. Application No. 09/261,922, and claims 36, 39, 40, 42, 44-46, 49, 50, 52, 54, and 55 of U.S. Application No. 09/934,207. Since the '416, '922, and '207 applications have not issued, Applicants will respond to these rejections if and when they are no longer provisional.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: March 6, 2003

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: March 6, 2003

Am. to #17

PATENT
Attorney Docket No. 213257

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kovesdi et al.

Application No. 09/964,065

Filed: September 26, 2001

For: REPLICATION-DEFICIENT ADENOVIRAL VECTOR AND PLASMID WITH ADENOVIRAL COMPONENT

Art Unit: 1632

Examiner: S.D. Priebe

AMENDMENTS TO CLAIMS
MADE IN RESPONSE TO OFFICE ACTION DATED DECEMBER 6, 2002

Amendments to existing claims:

48. (Three Times Amended) A defective recombinant adenovirus that (a) requires, for replication, complementation *in trans* of one or more essential gene functions of an E1 region and an E4 region of an adenovirus genome, and (b) comprises an adenoviral genome <u>having a deficiency of one or more essential gene functions of the E1 region, a deletion of the entire E4 region, and optionally a deletion of all or part of the E3 region</u> [wherein all or part of the E1 region and the whole of the E4 region, and optionally all or part of an E3 region, is deleted from the adenoviral genome].

[49. The defective recombinant adenovirus of claim 48, wherein part of the E1 region is deleted.]

50. (Amended) The defective recombinant adenovirus of claim 48, wherein [all of the E1 region is deleted] <u>the adenoviral vector comprises an adenoviral genome having a deficiency of all essential gene functions of the E1 region</u>.

[51. The defective recombinant adenovirus of claim 49, wherein all or part of the E3 region is deleted.]

53. (Amended) A system comprising:

(i) an adenoviral vector comprising an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions in either or both of the E2A region and the E4 region of the adenoviral genome, and optionally a deficiency in the E3 region of the adenoviral genome, and

(ii) a [293 cell or an A549] cell having a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions in either or both of the E2A region and the E4 region of the adenoviral genome,

wherein there is no overlap between the cellular genome and the adenoviral genome to mediate a recombination event between the cellular genome and the adenoviral genome.

55. (Amended) The system of claim 53, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions of the E4 region of the adenoviral genome, and the cell has a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions of the E4 region of the adenoviral genome.

[61. The system of claim 53, wherein the cell is a 293 cell.]

[62. The system of claim 53, wherein the cell is an A549 cell.]

63. (Amended) A method of propagating an adenoviral vector, which method comprises

(a) providing an adenoviral vector comprising an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions in either or both of the E2A region and the E4 region of the adenoviral genome, and optionally a deficiency in the E3 region of the adenoviral genome,

(b) providing a [293 cell or an A549] cell comprising a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions in either or both of the E2A region and the E4 region of the adenoviral genome, wherein there is

no overlap between the cellular genome and the adenoviral genome to mediate a recombination event between the cellular genome and the adenoviral genome, and

(c) propagating the adenoviral vector in the cell.

[71. The method of claim 63, wherein the cell is a 293 cell.]

[72. The method of claim 63, wherein the cell is an A549 cell.]

73. (New) The system of claim 53, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions of the E2A region of the adenoviral genome, and the cell has a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions of the E2A region of the adenoviral genome.

74. (New) The system of claim 73, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

75. (New) The system of claim 53, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions of both the E2A region and the E4 region of the adenoviral genome and the cell has a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions of both the E2A region and the E4 region of the adenoviral genome.

76. (New) The system of claim 75, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region; and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

77. (New) The system of claim 75, wherein the cellular genome comprises at least open reading frame (ORF) 6 of the E4 region of the adenoviral genome.

78. (New) The system of claim 77, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

79. (New) The system of claim 77, wherein the cellular genome comprises at least ORF6 and no other ORF of the E4 region of the adenoviral genome.

80. (New) The system of claim 79, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

81. (New) The method of claim 63, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions of the E2A region of the adenoviral genome, and the cell has a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions of the E2A region of the adenoviral genome.

82. (New) The method of claim 81, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

83. (New) The method of claim 63, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and a deficiency in one or more essential gene functions of both the E2A region and the E4 region of the adenoviral genome and the cell has a cellular genome that complements in *trans* for the deficiency in one or more essential gene functions of the E1 region of the adenoviral genome and the deficiency in one or more essential gene functions of both the E2A region and the E4 region of the adenoviral genome.

84. (New) The method of claim 83, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

85. (New) The method of claim 83, wherein the cellular genome comprises at least open reading frame (ORF) 6 of the E4 region of the adenoviral genome..

86. (New) The method of claim 85, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

87. (New) The method of claim 85, wherein the cellular genome comprises at least ORF6 and no other ORF of the E4 region of the adenoviral genome.

88. (New) The method of claim 87, wherein the adenoviral vector comprises an adenoviral genome having a deficiency in all essential gene functions of the E1 region, and the cell has a cellular genome that complements in *trans* for the deficiency in all essential gene functions of the E1 region.

89. (New) The defective recombinant adenovirus of claim 48, wherein the adenoviral genome is a human adenoviral genome.

90. (New) The defective recombinant adenovirus of claim 89, wherein the adenoviral genome is an Ad5 adenoviral genome.

91. (New) The system of claim 53, wherein the adenoviral genome is a human adenoviral genome.

92. (New) The system of claim 91, wherein the adenoviral genome is an Ad5 adenoviral genome.

93. (New) The system of claim 55, wherein the adenoviral genome is a human adenoviral genome.

94. (New) The system of claim 93, wherein the adenoviral genome is an Ad5 adenoviral genome.

95. (New) The method of claim 63, wherein the adenoviral genome is a human adenoviral genome.

96. (New) The method of claim 95, wherein the adenoviral genome is an Ad5 adenoviral genome.

97. (New) The method of claim 65, wherein the adenoviral genome is a human adenoviral genome.

98. (New) The method of claim 97, wherein the adenoviral genome is an Ad5 adenoviral genome.